NTP
National Toxicology Program

Report on Carcinogens
Draft Substance Profile on Captafol

Gloria D. Jahnke, DVM
National Institute of Environmental Health Sciences
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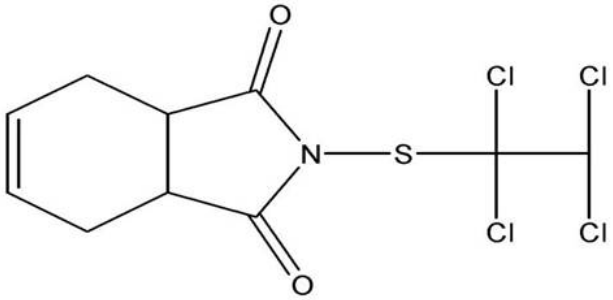
Captafol

CAS No. 2425-06-1



3a,4,7,7a-tetrahydro-2-[(1,1,2,2-tetrachloroethyl)thio]-1*H*-isoindole-1,3-(2*H*)-dione (CAS), difolatan (JMAF), 1,2,3,6-tetrahydro-N-(1,1,2,2-tetrachloroethylthio)phthalimide (IUPAC), N-(1,1,2,2-tetrachloroethylthio)cyclohex-4-ene-1,2-dicarboximide (IUPAC), 3a,4,7,7a,tetrahydro-N-(1,1,2,2-tetrachloroethanesulfenyl)phthalimide (IUPAC)

Objectives

To present the science that supports the preliminary listing recommendation for captafol in the 12th RoC as *Reasonably Anticipated to be a Human Carcinogen*

- Information on use and exposure in US
- Cancer studies in humans and experimental animals
- Mechanistic evidence that supports the recommendation

Uses

- Non-systemic fungicide used on fruits, vegetables, other plants, and timber products in US from 1961 until 1987
- Legal use of existing stocks until 1999, EPA restricted use to onions, potatoes, and tomatoes
- These remaining tolerances revoked by EPA in 2006

Exposure

- Potential exposure from consumption of imported food products containing residues
- Dermal, oral, and inhalation absorption
- Significant past occupational and environmental exposure

Human Cancer Studies

- Data from studies inadequate to evaluate relationship between human carcinogenicity and exposure to captafol
  - One ecological case control study of pancreatic cancer and organochlorine agents (18 pesticides)
  - Non-significant increase in pancreatic cancer in residents living for >20 years in areas with high captafol usage

Sufficient Evidence from Studies in Experimental Animals

Tumors at multiple sites in mice

- Chronic feed studies in CD-1 mice (110 wks) (Quest *et al.* 1993)
  - Lymphosarcoma, hemangiosarcoma (heart, liver, spleen, and subcutis), Harderian gland adenoma (males)
- Chronic feed studies in $B6C3F_1$ mice (surviving at least 42 wks) (Ito *et al.* 1984)
  - Hemangioendothelioma (heart), hemangioma (spleen), and tumors of the small intestine and liver

Sufficient Evidence from Studies in Experimental Animals

Tumors at multiple sites in rats

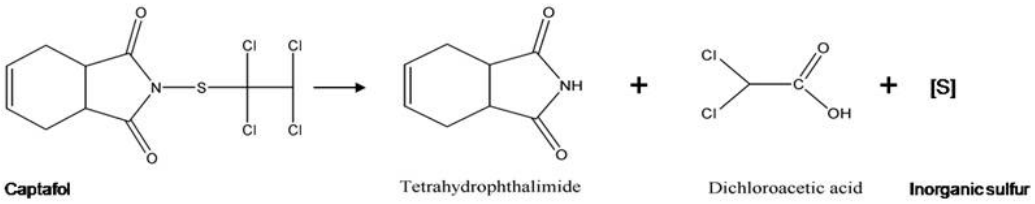
- Chronic feed studies in Crl:CD rats (2 yrs) (Quest *et al.* 1993)
  - Kidney tumors (males); mammary gland fibroadenomas and neoplastic nodules in the liver (females)
- Chronic feed studies in F344 rats (2 yrs) (Tomano *et al.* 1990, Nyska *et al.* 1989)
  - Kidney tumors and neoplastic nodules in the liver

Mechanistic Evidence

- Proposed bioactivation pathways
- Genotoxic endpoints
- Other effects

Bioactivation

- Hydrolysis of N-S chemical bond
- Proposed episulfonium ion intermediate formed from the side-chain



Captafol | Tetrahydrophthalimide | Dichloroacetic acid | **Inorganic sulfur**

Captafol is Genotoxic

Endpoint	Bacteria	Mammalian Cell Lines	*In Vivo*
Mutations	+	NT	+ (rat germ cell)
DNA single strand breaks		+	+
Sister chromatid exchange		+	NT
Chromosomal aberrations		+	NT
Micronucleus formation		+	+
Mitotic spindle disturbances		+	NT
Cell transformation		+	NT

NT = Not tested

Other Effects

- Cytotoxicity due to reaction of captafol with thiol-containing molecules such as glutathione and cysteine resulting in reduced cellular content of thiol groups
- Inhibition of enzymes involved in DNA replication and synthesis and RNA synthesis
- Induction of cytochrome P-450 monooxygenases

Proposed Captafol Listing

Captafol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting mechanistic data.